Chronic Lymphocytic Leukemia

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Case Study

- 57 year old male, trial application for $1,000,000 Universal Life coverage
- Cover letter from sales agent indicates client has Chronic Lymphocytic Leukemia (CLL) diagnosed in 1999 (age 44), and is on new medication, GA-101, which has been very successful
- Last 3 months of oncology treatment notes sent for review
  - Most recent 5/12 note indicates client with Rai stage II disease, showing improvement in lymphadenopathy, splenomegaly no longer detectable, and elimination of his "B" symptoms after 2 doses of GA-101
  - CBC normal other than slightly low platelet count (144,000/mm^3)

Case study, continued

- Oncology records, continued:
  - 3/12 labs, prior to starting GA-101 treatment:
    - Absolute lymphocyte count > 50,000/mm^3
    - Platelet count 112,000/mm^3
    - β-2 microglobulin 1,746 (no units given; usual normal range is less than 4 mg/L)
  - Prior evaluation included:
    - low CD38 and ZAP-70
    - 13q deletion in the leukemic cells on flourescent in-situ hybridization (FISH) testing
  - 5/12 treatment plan was to continue with planned 3rd dose of GA-101 and return in three weeks
- What are important points in risk assessment of this case?

USA – Estimated Leukemia New Cases and Deaths in 2012

- CLL is the most common form of leukemia in the USA

Type of leukemia	Estimated Cases	Estimated deaths
Acute lymphocytic	6,050	1,440
Chronic lymphocytic	16,060	4,580
Acute myeloid	13,780	10,200
Chronic myeloid	5,430	610
Other leukemias	5,830	6,710
Totals	47,150	23,540

American Cancer Society

CLL - Epidemiology

- SEER data, 1975 - 2009:
  - Incidence fairly stable @ 4-5/100,000/year
  - M:F ratio about 2:1
  - 5-year relative survival is improving:
    - Diagnosis in 1975 – 1977: 67.4%
    - Diagnosis in 2002 – 2008: 82.4%
- Primarily a disease of older aged persons
  - Median age at diagnosis is 72 yrs
  - 70% of patients are > 65 yrs at time of diagnosis
  - < 2% of patients younger than 45 yrs at diagnosis
- Incidence lower in Asia, Latin America and Africa than in North America and Western Europe

Clinical Presentation

- Many CLL patients asymptomatic, diagnosed on routine CBC
- Painless lymphadenopathy, often cervical area
- Systemic "B" symptoms of lymphoma (5-10%) are unfavorable when present
  - Unintentional weight loss > 10% over 6 mos
  - Fever or drenching night sweats without evidence of infection
  - Extreme fatigue

CLL Pathology

- Etiology unclear
  - 2 – 7X increased risk for family members of CLL patients
  - Possible role of certain agricultural chemicals
  - Monoclonal B-cell lymphocytosis (MBL)
    - Present in about 4% of the population > 40 yrs of age
    - All cases of CLL appear to be preceded by MBL, but most patients with MBL will not develop CLL or any other hematologic malignancy
    - Progresses to CLL at rate of 1-2%/year

CLL Pathology, cont'd

- CLL characterized by progressive accumulation of mature-looking lymphocytes in blood, bone marrow and lymphatic tissues
  - Cells are functionally immature
  - Cells indistinguishable from those in Small Lymphocytic Lymphoma (different manifestations of the same disorder in WHO classification)
- B-cell neoplasm
  - Positive for CD5 and CD23 cell surface markers

Differential Diagnosis of SLL, CLL and MBL

Disease	Peripheral Blood Lymphocytes	Bone Marrow Lymphocyte Infiltration (%)	Extramedullary Disease
CLL	≥ 5 x 10^9/L (≥ 5,000/mm^3)	≥ 30	Present or absent
SLL	< 5 x 10^9/L (< 5,000/mm^3)	< 30	Present
MBL	< 5 x 10^9/L (< 5,000/mm^3)	< 30	Absent

Hematology Oncology Clinics Oct 2008

Two Staging Systems

- Binet – more commonly used in Europe

  Stage A: No anemia or thrombocytopenia, fewer than three areas of lymphoid involvement

  Stage B: No anemia or thrombocytopenia, three or more areas of lymphoid involvement

  Stage C: Anemia (hemoglobin < 10 g/dl) and/or thrombocytopenia (< 100 x 10^9 or < 100,000/mm^3), regardless of the number of areas of lymphoid involvement

Rai Staging System

Stage 0: Lymphocytosis > 5 x 10^9 (>5,000/mm^3)

Stage I: Lymphocytosis with lymphadenopathy

Stage II: Lymphocytosis with hepatomegaly or splenomegaly, with or without lymphadenopathy

Stage III: Lymphocytosis with anemia (Hemoglobin < 11 g/dL) with or without lymphadenopathy, hepatomegaly or splenomegaly

Stage IV: Lymphocytosis and thrombocytopenia (<100,000/mm^3), with or without other features

Median Survival by Stage

Stage	Median Survival (years)
Rai Stage 0	14.5
Rai Stage I & II	7.5
Rai Stage III & IV	2.5
Binet Stage A	14
Binet Stage B	5
Binet Stage C	2.5

Hematology Oncology Clinics Aug 2009

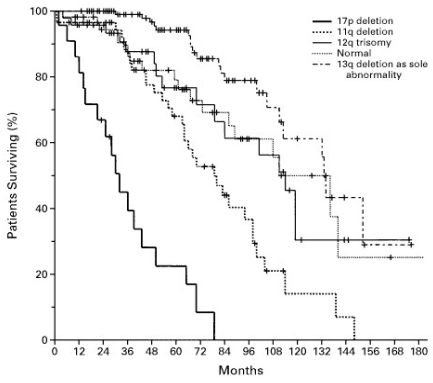
Other Unfavorable Prognostic Factors

- Advanced age
- Male gender
- Lymphocyte doubling time < 12 months
  - Shortened median survival time (36 months)
- Beta 2 microglobulin elevated
  - Reflects tumor burden and cell turnover rate
- CD38 positivity (≥ 30% of leukemic cells)

Cytogenetic Abnormalities

- Using flourescence in-situ hybridization (FISH) cytogenetic abnormalities present in 82% of CLL patients
- Favorable: 13q deletion as sole abnormality
- Neutral: Trisomy 12
- Unfavorable:
  - 17p deletion – very aggressive clinical course
  - 11q deletion

Probability of Survival from the Date of Diagnosis among the Patients in the Five Genetic Categories.



No. at Risk															
17p deletion	23	18	13	8	5	4	1	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0	0
12q trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	1	0
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1	0

Döhner H et al. N Engl J Med 2000;343:1910-1916.

IgV_H Gene Mutation

- Mutations in immunoglobulin heavy chain variable gene (> 2% difference from germ-line) are associated with longer survival
  - Seen in approximately 50% of CLL patients
  - Median survival of 293 months versus 95 months for patients with unmutated IgV_H (Hamblin et al *Blood* 2005;94: 1848-54)
- Determination requires DNA sequencing
  - Expensive, and not readily available

Next best thing: ZAP-70

- Zeta chain associated protein 70 – a tyrosine kinase involved in cellular signaling in T cells
  - Measured by flow cytometry, which is widely available
- Abnormally expressed in malignant B cells of some patients with CLL
  - Said to be overexpressed when present in >20% of cells
- Overexpression correlates with unmutated IgV_H and and portends similarly worse prognosis

Treatment of CLL/SLL

- Watchful waiting appropriate for many asymptomatic patients without rapid disease progression
  - Exception: Patients with 17p deletions
  - In other patients, indications for treatment include systemic symptoms, progressive marrow failure, autoimmune cytopenias, massive splenomegaly or lymphadenopathy and rapid lymphocyte doubling time
- Radiation therapy – treatment of choice for rare patients with Ann Arbor Stage 1/2 SLL
  - 10 yr relapse-free survivals of 80% for stage 1 and 62% for stage 2 (Morrison et al, J Clin Oncol 1989)

Chemotherapy for CLL

- Effectiveness varies with prognostic factors
  - Palliative, not curative
- Multi-agent: alkylator + nucleoside analog
  - Fludarabine and cyclophosphamide (FC) most often used
- Single agents used in more frail patients
  - Chlorambucil, fludarabine, bendamustine all have good activity as single agents
- Immunomodulatory drugs (lenalidomide) also active as single agents and in combination with immunotherapy (monoclonal antibodies)

Monoclonal Antibodies

- Rituximab – acts against CD20 cell surface antigen, which is present on > 90% of mature B-cell leukemias and lymphomas
  - Has single agent activity against CLL
  - Most often combined with FC --> FCR
    - Standard of care in young (< 70 years) healthy patients
    - Response rates of 76% with progression free survival rates of about 40 months in clinical trials (Shansal M, Haddad R, Dis Mon 2012)
- Alemtuzumab – anti-CD52 agent recently approved for CLL
  - Effective agent; studies ongoing
  - Combined with high dose methylprednisolone, is a good first-line treatment for patients with 17p deletion

Stem Cell Transplantation

- Usually reserved for younger patients with unfavorable features (unmutated IgV_H, 17p or 11q deletions)
- Allogeneic Hematologic Cell Transplantation (allo-HCT) most effective
  - Graft-vs-leukemia effects of donor cells largely responsible, but also cause undesirable graft-versus-host disease issues
  - Reduced intensity conditioning programs decrease transplant related mortality but may increase relapse risk
- Durable remissions (cures) are possible

Case Study Wrap-Up

- Unfavorable features:
  - Male, 13 years into course of disease
  - Rai stage II (Binet B) with early thrombocytopenia
  - High β-2 microglobulin
- Favorable features:
  - Cytogenetics (13q deletion) and low CD38 and ZAP-70
  - Age?
  - Excellent response to GA-101 (obinutuzumab), a 3rd generation anti-CD20 monoclonal antibody
    - Early studies look like it may be more effective against B-cell malignancies than rituximab
    - Long term survival statistics not yet available

CLL - Summary

- Most common form of leukemia in USA
- Usually presents at ages > 60 years
- Course is often quite indolent, but can occasionally be progressive over far fewer years
- Best cases characterized by:
  - Early stage (Rai 0, Binet A)
  - Slow lymphocyte doubling time
  - Cytogenetics normal, trisomy 12 or 13q deletion as sole abnormality
  - IgV_H mutated; low ZAP-70, CD-38 and beta-2-microglobulin
- Survivals are improving with newer treatments, but most still considered palliative, as few cases are cured

The doctor gave a woman six months to live.

She couldn't pay her bill, so she gave her another six months!